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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING NATURAL HUMAN α-INTERFERON

(57) Abstract

Use of natural human α-interferon for the preparation of a medicament in liquid form to be administered through peroral route at dosages comprised between 100 UI and 500 UI/day, for therapy of viral infections, in particular viral hepatitis, neoplasia and immune diseases in humans and animals.

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PHARMACEUTICAL COMPOSITIONS COMPRISING NATURAL HUMAN α-INTERFERON

The invention concerns pharmaceutical compositions for a peroral administration comprising natural human α-interferon isolated from lymphoblastoid or leukocitic cells. In particular compositions are useful for therapy of viral infections, in particular viral hepatitis, neoplasia and immunodeficiency syndromes. The interferon efficient dosages are clearly lower than dosages utilized for parenteral administration.

α-, β-, γ-interferons are usually administered by injection and are used for therapy. α-interferon is the most largely utilized interferon (1). In an updated study of medicaments for either acute or chronic viral hepatitis therapy (2), only α-interferon is widely accepted as single therapeutic agent.

"Viral hepatitis" means at least five different pathologies, having different agents, namely A, B, C, D, E.

The therapeutic trend is to treat said pathologies with α-interferon, with dosages according to the kind of hepatitis, to the overall status of the subject and to other variable factors. In general, further to the interferon treatment an almost normalisation clinical and biochemical parameters is achieved for chronic hepatitis (B, C, D). The interferon activity on acute hepatitis has not been focused yet, though for hepatitis C, a therapeutic treatment with α-interferon lowers the chronicition rate of the disease.

Therapeutic cycles indicate the day alternate administration through subcutaneous route of recombinant α-interferon (r α-IFN) at dosages of app. 5.000.000 UI, that in special cases can be up to 9.000.000 UI/day.

The length of therapeutic cycles is of from six months up to one year (nine months average).

In many cases, undesired side effects interfere with the course of therapeutic treatment. In fact some patients, in particular those at an advanced stage of disease or with severe physiologic damages, do not tolerate the therapy and therefore the treatment should be interrupted. Claimed side effects are: fever, nausea, vomit, tiredness, algia and depression.

Moreover the therapeutic cost are quite relevant both due to the high amount of active principle (more than 8.000 new cases each year in Italy and 300.000 world-wide) and to the necessity of hospitalisation just in consideration of said side effects further to the parenteral administration (day hospital or outpatients' department).

Finally, as far as chronic active viral hepatitis the only alternative to the interferon treatment is represented by liver transplant.

The clinical trend is to increase the posology dosage and the length of therapeutic cycle (3), but clinical data show (4): severe side effects; low acceptance by the patient; high therapeutic costs. Garcia et al. (5) report that the estimate for each cured patient is between 700.000 and 2.000.000 English pounds Capri S. (6) report that the cost of each interferon therapeutic treatment is of Lit. 70.000.000/subject.

It is therefore evident that the actual composition of interferon for therapeutic treatment of hepatitis is not optimal.

Moreover clinical results show a better therapeutic efficacy in patients which are not the main target for therapy, namely: young subjects, subjects with a disease at an initial stage, subjects infected with genotipic virus 2 or 3, low viremia subjects. On the contrary a less therapeutic efficacy can be found in those subjects which really need the therapeutic treatment (subjects poco respondent), as subjects affected by an aggressive

form (active chronic hepatitis), long length diseases affected subjects, over 50 subjects. Thus patients that really need an immediate interferon treatment are those that have a lower chance of success (7).

The authors of the instant invention have found a pharmaceutical composition comprising natural human α-interferon from either lymphoblastoid or leukocitic cells to be administered through peroral route, with dosages clearly lower than those used for parenteral administration. The composition maintains as unaltered chemical-physical, biological and pharmacological characteristics of the active principle, having a therapeutic effect substantially analogous to the compositions of prior art but overcoming disadvantages thereof.

The composition is preferably in a liquid form with a concentration of 100 to 500 UI/ml, preferably approx. 150 UI/ml, most preferably in mono-dosage units, most preferably of appr. 1 ml.

The composition acts by activating the defence mechanisms against viral infections, tumour growth and stimulates an immune response.

The utilisation of natural interferon was chosen for the better chances of therapeutic success with respects to recombinant interferon, obtained by cloning of a single subtype.

Though leukocitic and lymphoblastoid interferons exert the same therapeutic properties, the former can be advantageously produced. As a matter of fact it is obtainable by stabilised cell lines, without the need of blood donors.

Processes for purifying interferons are known to those skilled in the art, and for example are shown in US Patent 4,732,683; in Cantell K. and Hirvonen S. Texas Reports on Biology and Medicine, Vol. 35, p.138, 1977; in Zoon K.C. et al. Science 207, p. 527, 1980.

The peroral route is generally much more accepted by subjects, makes easier posology schemes and dosages, lowers to stops the antigenic risk, induces the transmission and amplification signal mechanism, with a mirato therapeutic effect, with dosages 100 times lower than known formulations for parenteral administrations.

The low dosage annuls the risk of toxic effects; allows a better availability of medicine to satisfy an increasing request and a drastic lowering of therapeutic costs.

The preferred formulation in dosage units of small volumes (1 ml) to drink allows an immediate availability of the active principle, a good standard of cleanliness from the monodosage primary container; the certainty of the taken dosage; the taking of the active principle to be immediately adsorbed by the oro-pharyngeal mucosa, easily preventing the deglutition, an ease and safe way of administration for all of patients, as opposite to lozenges or tablets formulations that should be kept in the mouth till to full dissolution, with high chances of swallowing.

Moreover the composition of the invention is conveniently used for home therapies or on the job place, as precautionary measure for the prophylaxis of viral pathologies, and to control chronic diseases which need of long therapeutic cycles (even yearly) and often recurrent.

The composition can be used also in association with other drugs to get synergism and optimize therapeutic schemes.

The following clinical studies show the therapeutic effect. A comparison of the electrophoretic protein pattern and of the concentration of IgG, IgA, IgM, before the beginning of the peroral therapy with natural human α-interferon of hepatitis or other pathologies affected subjects, before and after two weeks of therapeutic

treatment, allows to foreseen quali-quantitatively the subject response.

Subjects which respond to the therapy with 450UI/die dosages show a decrease of α2- and ß-globulins, of IgGs, of the IgG/IgA ratio, together to an increase of IgA and IgM concentrations, have a good chance of eliminate the HBVe antigen and to seroconvert, namely to confer a stable remission of the pathology.

On the other hand subjects which respond to the same therapy with a decrease of albumin serum concentration, of IgGs, IgAs, IgMs, together to an increase of α1-globulin fractions, should seronvert with longer times.

Moreover subjects that respond with an increase of IgGs, of the IgG/IgA ratio, together to a decrease of IgM and of the IgA/IgM ration, could be resistant to the therapy.

The monitoring of said parameters (markers) is useful for a planning of therapeutic strategies in clinic and also for the clinical practitioner.

Clinical studies on healthy subjects

Table 1 shows different therapeutic schemes.

Table 1

Exp.		active comp.	No. admin. /day	Dosages	days trt.	blood bleedings
A	aA	α-IF	1(3dsg)	450 UI	1	$T_0, T_1, T_2, T_3,$
	aB	placebo	1(3dsg)	-	1	T_0, T_1, T_2, T_3
B	bA	α-IF	1(3dsg)	450 UI	5	$T_0, T_1, T_2, T_3, T_4,$ $T_5, T_6, T-$
	bB	placebo	1(3dsg)	-	5	$T_0, T_1, T_2, T_3, T_4,$ $T_5, T_6, T-$
C	cA1	α-IF	2(1dsg)	300 UI	1	T_0, T_1, T_2, T_3
	cA2	α-IF	3(1dsg)	450 UI	1	T_0, T_1, T_2, T_3
	cb	placebo	3(1dsg)	-	1	T_0, T_1, T_2, T_3
D	dA1	α-IF	2(1dsg)	300 UI	5	$T_0, T_1, T_2, T_3, T_4,$ $T_5, T_6, T-$
	dA2	α-IF	3(1dsg)	450 UI	5	$T_0, T_1, T_2, T_3, T_4,$ $T_5, T_6, T-$
	dB	placebo	3(1dsg)	-	5	$T_0, T_1, T_2, T_3, T_4,$ $T_5, T_6, T-$

T_0 = background; T_1 = 1d further the first administration, T_2 = 2d further the first administration, T_3 = 3d further the first administration, T_4 = 4d further the first administration, T_5 = 5d further the first administration, T_6 = 1d after the treatment suspension, T_7 = 2d after the treatment suspension.

The change of the induced biological response with respect to the therapeutic scheme, has been measured on samples of blood, taken at different times. In particular the activity with respect to the day dosage of active principle, to the mono- or pluri-administration, to the length of the therapeutic cycle was measured.

The analysis of data show that natural human α-interferon from either lymphoblastoid or leukocitic cells, administered at low dosages for a peroral route, is able to modulate (according to the dosage and to the length of the therapeutic cycle) the expression of membrane antigen of healthy subject blood mononuclear cells. In particular, according to therapeutic scheme, the pharmaceutical composition seems to be able to increase both CD4 and CD8 cell population. It is also evident an increased expression of markers of cell activation, as DR antigens and interleukin 2 receptor.

The therapeutic scheme with 450 U/die x 5 d (exp.b) is the one provided better results, as shown in Tables 2 and 3. In fact there is an increase (% and absolute) of CD3, CD4, DR1, CD25 lymphocytes. Said increases are, according to different cases, better evident at T_3, T_4, T_5 times to later decrease at T_6 and T_7 times.

The same posology dosage, but with a shorter therapeutic cycle (1 day) (exp.a), interferes less evidently with the % and absolute numbers of mononuclear cells in the blood (Tables 4 e 5). In fact in this experiment an increase of average percentage values but not of absolute T, CD8, and class II hystocompatibility antigen lymphocytes values, is evident at time T_3.

Other experimental conditions show lower increases of the immune response.

Therefore, natural human α-interferon from either lymphoblastoid or leukocitic cells, administered at low dosages trough peroral route, shows an important role in modulating the immune response, both in the phase afferent than efferent, e has a therapeutic application for the treatment of infective diseases and of other conditions of immunodeficiency.

Clinical studies on hepatitis subjects

Viral B Hepatitis

14 patients affected by chronic viral B hepatitis, with an age comprised between 4 and 59, were used for randcm studies.

All of subject were previously treated for different periods ranging from some months to some years with steroids, or with steroid-azothiopurine, with no beneficial effects, neither for the clinical symptomatology nor for the biochemical parameters of the disease, which evolved, in some cases, to hepatic cirrhosis.

The therapeutic treatment of a one administration of 150U/day was initiated immediately after the suspension of the previous treatment, and effects of said treatment were monitored by checking any alteration of the immune response; of the haematological and biochemical parameters; of serum markers of the viral infection and of the hystochemistry of hepatic bioptic samples.

The time of observation varied from 15 to 32 months and results can be summarized in the following:

1) all of patients during the first 3-6 weeks of treatment registered a transient decay of hepatic biochemical functions (i.e. a 2-3 fold increase of alanineaminetransferase (ALT) levels), with no clinical symptoms of disease worsening;

2) the phenomenon goes on for 4-6 weeks;

3) in all of treated patients an intense activation of the immune system was observed, even after the therapeutic treatment;

4) 7 patients eliminate HBV DNA and HBeAg from serum and stable seroconvert;

5) 1 patient has an HBcAg increased title, more than the original value;

6) in other 9 patients said titre decreases significatively.

Therefore, 50% of patients get a stable remission of the disease.

Viral C Hepatitis

The therapeutic standard of viral hepatitis C foresees the use of α-interferon through parenteral route.

6 active chronic hepatitis C affected patients were subjected to therapy with peroral administration at 150U/die, by starting the treatment just after the suspension of the steroid therapy.

The observation time (equal to the length of the treatment) resulted to be variable from 19 to 69 weeks. In general the treatment was well tolerated and all of patients registered a significant increase of vivacity and appetite, with a better tolerance to physical exercises.

No patients got a normalization of transaminase levels during the observation period, but one which registered the biochemical and clinical remission of the disease, after the treatment suspension at the 19th week due to an increasing of articular pains.

Results are shown in tables 2-5.

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TREATMENT	TIME	%CD3	%CD4	%CD8	%CD25	%MHCII	%B	%NK	%CD14
450UI/d x 5d 3ds	T_0	69,2±4,9	42,8±4,3	26,3±2,9	1,4±0,9	7,5±0,8	11,5±1,1	6,9±0,7	10,3±1,6
PLACEBO x 5d 3ds	T_0	71,3±5,2	41,7±4,1	24,5±3,5	<0,5	8,1±1,2	13,1±1,6	8,1±1,3	9,3±1,2
450UI/d x 5d 3ds	T_1	70,1±5,1	43,1±4,5	25,8±3,1	<0,5	8,2±1,3	12,1±1,4	7,2±1,3	3,9±1,4
PLACEBO x 5d 3ds	T_1	72,4±5,4	40,8±3,9	25,3±3,8	<0,5	8,7±1,4	12,7±1,8	8,2±1,5	10,1±1,3
450UI/d x 5d 3ds	T_2	70,2±5,1	44,2±3,1	23,2±3,1	1,7±1,3	9,1±1,3	12,5±1,6	7,1±0,9	11,1±1,5
PLACEBO x 5d 3ds	T_2	70,8±5,3	41,1±4,2	24,7±3,7	1,2±0,9	8,7±1,4	11,4±1,6	6,9±1,9	10,8±1,7
450UI/d x 5d 3ds	T_3	69,8±5,7	49,4±4,9	24,1±3,6	2,5±1,6	14,2±1,3	12,1±1,4	7,2±1,1	9,7±1,8
PLACEBO x 5d 3ds	T_3	71,3±5,6	41,5±4,3	24,4±3,5	<0,5	8,5±1,3	13,1±1,8	6,9±1,7	10,1±1,8
450UI/d x 5d 3ds	T_4	72,3±5,8	49,7±5,1	23,8±3,8	2,3±1,7	14,2±2,5	12,5±1,8	6,8±0,9	9,4±1,5
PLACEBO x 5d 3ds	T_4	69,8±5,3	40,9±4,2	25,2±4,3	<0,5	7,9±0,9	12,9±1,9	7,1±0,7	11,6±2,1
450UI/d x 5d 3ds	T_5	71,8±5,4	53,3±4,9	74,2±4,1	2,5±1,6	14,2±1,9	13,5±2,1	7,3±0,9	11,3±1,6
PLACEBO x 5d 3ds	T_5	70,6±5,5	41,3±4,1	25,9±4,4	1,4±1,3	8,1±1,3	12,6±1,4	7,5±0,9	9,9±2,3
450UI/d x 5d 3ds	T_6	69,7±5,2	50,7±4,7	23,7±4,1	1,6±0,9	11,3±1,5	12,8±1,9	6,9±0,6	10,8±1,9
PLACEBO x 5d 3ds	T_6	71,3±5,6	42,3±4,3	24,7±3,8	<0,5	7,9±1,4	11,4±1,1	7,3±0,5	10,4±1,9
450UI/d x 5d 3ds	T_7	70,2±5,1	45,3±4,4	24,2±3,8	1,1±0,9	8,7±1,1	12,3±1,6	7,1±0,7	11,2±7,1
PLACEBO x 5d 3ds	T_7	71,5±5,8	41,5±3,9	25,1±4,1	<0,5	8,1±1,6	11,9±1,4	7,8±0,8	9,8±1,7

b vs a = $p<0,05$; c vs a = $p<0,01$; e vs d = $p<0,01$; f vs d = $p<0,05$ Student's "t" test

Tab. 2 -

TREATMENT	TIME	CD3 n°/mm³	CD4 n°/mm³	CD8 n°/mm³	CD25 n°/mm³	MHCII n°/mm³	B n°/mm³	NK n°/mm³	CD14 n°/mm³
450UI/d x 5d 3ds	T_0	1776±323	1074±108	560±145	35±23	188±60	288±87	173±88	177±78
PLACEBO x 5d 3ds	T_0	1658±220	970±195	565±171	<13	188±68	305±77	188±90	203±88
450UI/d x 5d 3ds	T_1	1858±128	1142±213	684±95	<13	217±53	320±65	191±73	213±95
PLACEBO x 5d 3ds	T_1	1784±195	1005±191	623±182	<13	214±73	313±142	302±85	216±90
450UI/d x 5d 3ds	T_2	1988±130	1251±115	657±98	48±33	258±43	354±70	301±73	196±138
PLACEBO x 5d 3ds	T_2	1746±183	1034±197	594±182	30±20	215±103	281±87	170±84	205±140
450UI/d x 5d 3ds	T_3	1878±132	1339±223	648±190	67±40	382±65	326±65	194±78	243±75
PLACEBO x 5d 3ds	T_3	1555±190	905±230	530±81	<11	185±130	286±52	150±99	234±72
450UI/die x 5d 3ds	T_4	1994±178	1325±168	539±195	62±43	381±90	336±145	183±75	187±48
PLACEBO x 5d 3ds	T_4	1733±213	1138±197	701±200	<14	230±121	359±174	198±76	167±69
450UI/d x 5d 3ds	T_5	2001±175	1456±283	579±203	70±40	399±108	379±88	205±73	197±140
PLACEBO x 5d 3ds	T_5	1720±226	1007±195	531±132	34±31	197±115	307±153	183±71	196±731
450UI/d x 5d 3ds	T_6	1719±170	1238±175	585±170	39±23	379±138	316±84	170±75	213±68
PLACEBO x 5d 3ds	T_6	1578±230	736±300	547±138	<11	175±132	252±126	162±62	242±74
450UI/d x 5d 3ds	T_7	1704±128	1058±170	586±105	27±23	211±128	298±97	172±78	197±83
PLACEBO x 5d 3ds	T_7	1595±235	924±191	559±195	<11	180±51	265±133	174±65	228±90

b vs s = $p<0,05$; d vs c = $p<0,05$; f vs c = $p<0,01$ Student's "t" test

Tab. 3 -

TREATMENT	TIME	%CD3	%CD4	%CD8	%CD25	%MHCII	%B	%NK	%CD14
450UI/d x 1d 3ds	T_0	70,3±5,7	42,4±3,8	25,3±2,6	1,7±1,4	7,2±0,8	9,7±1,4	8,4±0,9	8,4±0,7
PLACEBO x 1d 3ds	T_0	69,9±5,3	43,8±4,2	24,3±2,7	<0,5	7,9±0,9	10,9±1,7	7,8±0,8	9,8±0,9
450UI/d x 1d 3ds	T_1	69,4±5,5	43,9±4,5	24,8±1,9	<0,5	8,3±1,3	10,5±1,7	9,3±2,1	8,3±0,8
PLACEBO x 1d 3ds	T_1	70,2±5,9	43,5±4,4	23,8±2,5	<0,5	8,2±1,3	11,2±1,8	7,3±1,2	8,5±0,6
450UI/d x 1d 3ds	T_2	73,6±6,1	43,5±4,3	27,3±3,1	<0,5	8,1±1,2	11,2±2,1	10,7±4,5	9,3±1,5
PLACEBO x 1d 3ds	T_2	70,1±5,6	44,1±4,7	24,7±3,1	1,4±0,9	7,7±1,4	12,1±2,7	8,1±0,9	8,8±1,3
450UI/d x 1d 3ds	T_3	77,8±6,2	44,1±4,8	2,7±2,4	2,3±1,9	11,2±1,5	10,9±1,9	8,3±0,7	12,2±3,1
PLACEBO x 1d 3ds	T_3	70,3±5,4	43,9±5,1	24,7±3,3	<0,5	8,1±0,9	10,5±1,7	8,5±1,6	10,7±1,4

b vs a = $p<0,01$; c vs d = $p<0,05$; e vs f = $p<0,05$ Student's "t" test

Tab. 4 -

TREATMENT	TIME	CD3 n°/mm³	CD4 n°/mm³	CD8 n°/mm³	CD25 n°/mm³	MHCII n°/mm³	B n°/mm³	NK n°/mm³	CD14 n°/mm³
450UI/d x 1d 3ds	T_0	1521±223	917±182	547±156	37±30	156±77	210±80	182±80	182±75
PLACEBO x 1d 3ds	T_0	1615±222	1012±197	561±162	<12	183±81	252±99	180±86	210±81
450UI/d x 1d 3ds	T_1	1501±218	949±189	536±141	<11	180±128	227±97	201±57	192±79
PLACEBO x 1d 3ds	T_1	1637±236	1014±202	555±188	<12	191±80	261±72	170±89	177±63
450UI/d x 1d 3ds	T_2	1587±132	938±183	589±97	<11	175±126	242±85	230±98	215±72
PLACEBO x 1d 3ds	T_2	1723±329	1083±189	607±172	34±21	189±82	297±62	199±71	206±80
450UI/d x 1d 3ds	T_3	1654±234	940±184	631±101	49±41	238±124	231±91	176±76	234±67
PLACEBO x 1d 3ds	T_3	1673±124	1045±178	588±76	<12	193±91	250±49	202±94	251±82

b vs a = $p<0,05$; d vs c = $p<0,05$; f vs e = $p<0,01$ Student's "t" test

Tab. 5 -

CLAIMS

1. Use of natural human α-interferon for the preparation of a medicament in liquid form to be administered through peroral route at dosages comprised between 100 UI and 500 UI/day, for therapy of viral hepatitis in humans and animals.

2. Use of natural human α-interferon for the preparation of a medicament in liquid form to be administered through peroral route at dosages comprised between 100 UI and 500 UI/day, for therapy of neoplasia and immunologic diseases in humans and animals.

3. Use of natural human α-interferon according to claims 1 or 2 wherein said interferon is obtained from lymphoblastoid cell cultures.

4. Use of natural human α-interferon according to claims 1 or 2 wherein said interferon is obtained from lymphocyte cells.

5. Use of natural human α-interferon according to any of previous claims wherein said medicament is administered in mono dosage units of appr. 1 ml.

6. Pharmaceutical liquid composition for peroral administration comprising natural human α-interferon either from lymphoblastoid cell cultures or from lymphocyte cells at a concentration between 100 UI/ml and 500 UI/ml.

INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/IT 97/00040

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/21

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 88 03411 A (AMARILLO CELL CULTURE COMPANY) 19 May 1988 see the whole document ---	1-6
X	ARCHIVUM IMMUNOLOGIAE ET THERAPIAE EXPERIMENTALIS 41 (3-4). 1993. 259-265, XP000674716 GEORGIADES J A: "Early changes in the plasma proteins of patients treated with low doses of oral natural human interferon alpha (IFN -alpha)." see the whole document --- -/--	1-6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
13 June 1997	07.07.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Moreau, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,X	ARCHIVUM IMMUNOLOGIAE ET THERAPIAE EXPERIMENTALIS 44 (5-6). 1996. 359-366, XP000674715 ZIELINSKA W ET AL: "Comparison of the long-term effects of treatment with oral and parenteral interferon alpha in chronic viral hepatitis patients." see the whole document -----	1-6

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter[illegible]ial Application No
PCT/IT 97/00040

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